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(54) Title: IMPROVED METHOD OF TREATING TYPE II DIABETES AND OBESITY

(57) Abstract: Disclosed is a method of agonizing the beta 3 receptor in a subject in need thereof. The method comprises administering to the subject between about 1.0 to about 5.0 milligrams per kilogram of body weight per day of a compound represented by Structural Formula (I) or (VIII). Preferably, between about 2.0 to about 5.0 milligrams, more preferably 2.0 to about 4.8 milligrams, and even more preferably between about 3.0 to about 4.8 milligrams per kilogram of body weight per day of a compound of formula (I) or (VIII) are administered.

IMPROVED METHOD OF TREATING TYPE II DIABETES AND OBESITY

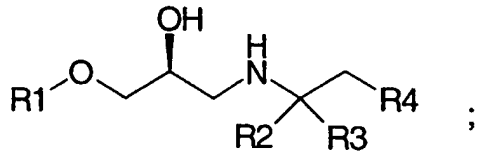
BACKGROUND OF THE INVENTION

Extensive research efforts are currently being devoted to the search for new drugs for the treatment of obesity and Type II diabetes. Beta 3 adrenergic agonists, including aryloxy propanolamines (see, for example, WO 97/10822 to Bell *et al.*, WO 98/09625 to Crowell *et al.*, and U.S. Patent No.'s 5,808,080 and 6,046,227), are one example of a promising new class of biologically active agents which can be used to treat these diseases.

A difficulty that is frequently encountered in treating patients with obesity or Type II diabetes is that these diseases are often associated with co-morbid diseases. Cardiovascular diseases, including but not limited to cardiac abnormalities such as atrial and ventricular tachycardia, angina, fibrillation, flutter, congestive heart failure (systolic and diastolic) and atrioventricular nodal reentry are among the more common and serious complications. The medications currently used to treat obesity and Type II diabetes are generally ineffective in treating and, more importantly, preventing cardiovascular disease. Consequently, it would be advantageous to develop therapies for obesity and/or Type II diabetes that can simultaneously treat or prevent cardiovascular disease.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method for agonizing the beta 3 receptor which comprises administering to a subject in need thereof about 1.0 to about 5.0 milligrams per kilogram body weight of said subject, a compound of formula I:



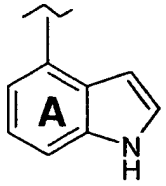
;

I;

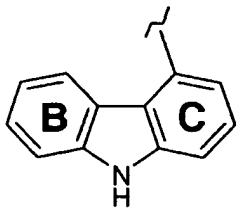
or a physiologically acceptable salt thereof,

wherein:

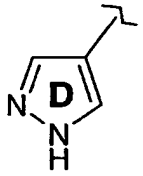
R1 is a moiety of the formula II, III, IV, V or VI:



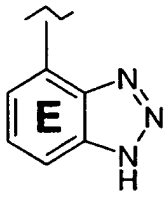
II



III



IV



V

VI

R2 and R3 are independently -H or C1-C4 alkyl;

R4 is optionally substituted phenyl provided that when R1 is a substituted moiety of formula VI, then R4 is substituted;

Ring **A** through Ring **E** are independently optionally substituted one or more times independently with a moiety selected from the group consisting of: halo, hydroxy, C1-C4

alkyl, C1-C4 haloalkyl, aryl, -CN, -COOR10, -CONHR10, -CONR10R10, -NHCOR10, -OR10, -NHR10, -SR10, $-SO_2R10$, $-SO_2NHR10$ or -SOR10;

Ring **F** is substituted with a group selected from halo, C1-C4 alkyl, hydroxyl, $-SO_2NHR5$, $-CO_2R5$, -CONHR5, $-CF_3$, $-CF_2H$, -NHCOR5 and NH(optionally substituted aryl);

R5 and R6 are independently hydrogen, C1-C4 alkyl or aryl;

R7 and R8 are independently hydrogen, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or R7 and R8 combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

R9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl or $(CH_2)_n$ optionally substituted heteroaryl;

R10 is independently hydrogen, C1-C4 alkyl or aryl; and

n is 0, 1 or 2.

Moreover, the present invention relates to a method for treating obesity or Type II diabetes which comprises administering to a subject in need thereof about 1.0 to about 5.0 milligrams per kilogram body weight of said subject a compound of formula I, or a physiologically acceptable salt thereof.

In addition, the present invention relates to the use of a compound of formula I, or a physiologically acceptable salt thereof, in the preparation of a medicament adapted for agonizing the beta 3 receptor or for treating obesity or Type II diabets characterized in that the medicament is such as to provide from about 1.0 milligrams per kilogram body weight to about 5.0 milligrams per kilogram body weight to a subject.

The present invention further relates to a pharmaceutical composition containing a compound of formula I, or a physiological salt thereof, adapted for administration of about 1.0 milligrams per kilogram body weight to about 5.0 milligrams per kilogram body weight in order to stimulate the beta 3 receptor or to treat obesity or Type II diabetes.

DETAILED DESCRIPTION OF THE INVENTION

A "subject" is preferably a human. However, a "subject" can also be an animal in need of such treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

A "subject in need of beta 3 receptor stimulation" is a subject for whom a beneficial therapeutic or prophylactic outcome can be achieved by agonizing some or all of the subject's beta 3 receptors. For example, subjects can be therapeutically or prophylactically treated for obesity or Type II diabetes by the administration of beta 3 agonists. The use of the beta 3 agonists disclosed herein for the treatment of obesity and Type II diabetes is described in greater detail in WO 97/10822 to Bell *et al.*, WO 98/09625 to Crowell *et al.*, U.S. Patent No. 5,808,080 and U.S. Patent No. 6,046,227, the entire teachings of which are incorporated herein by reference.

The term "aryl" includes carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthacyl.

The term "heteroaryl" includes monocyclic rings such as *N*-imidazolyl, 2-imidazole, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidy, 4-pyrimidyl, 2-pyranyl, 3-pyranyl, 3-pyrazolyl, 4-pyrazolyl,

5-pyrazolyl, 2-pyrazinyl, 2-thiazole, 4-thiazole, 5-thiazole, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Heteroaryl groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazole, 2-benzooxazole, 2-benzimidazole, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, and acridintyl.

Also included within the scope of the term "aryl group" or "heteroaryl group" is a group in which one or more carbocyclic aromatic rings and/or heteroaromatic rings are fused to a cycloalkyl or non-aromatic heterocyclic ring. Examples include decalin, phthalimido, benzodiazepines, benzooxazepines and benzooxazines and phenothiazines.

The terms "substituted phenyl" and "substituted cycloalkyl" refer to a phenyl or cycloalkyl group that is substituted one or more times independently with a moiety selected from the group consisting of halo, -CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OR9, -CO_2R6, -CONR7R8, -CONH(C1-C4 alkyl), -SR6, -CSNHR6, -CSNR7R8, -SO_2R6, -SO_2NR7R8, -SOR6, -NR7R8, optionally substituted aryl, optionally substituted heteroaryl, or C2-C4 alkenyl substituted with -CN, -CO_2R2 or -CONR7R8.

The terms "substituted aryl" and "heteroaryl" refer to an aryl or heteroaryl group that is substituted one or more times independently with a moiety selected from the group consisting of halo, -CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OR9, -CO_2R6, -CONR7R8, -CONH(C1-C4 alkyl), -SR6, -CSNHR6, -CSNR7R8, -SO_2R6, -SO_2NR7R8, -SOR6, -NR7R8, or C2-C4 alkenyl substituted with -CN, -CO_2R2 or -CONR7R8.

It has now been found that certain beta 3 receptor agonists, specifically certain aryloxy propanolamines, can

block the effects of compounds which produce tachycardia. Some of these beta 3 receptor agonist aryloxy propanolamines are partial agonists/antagonists at the tachycardia receptor and cause only slight increases in heart rate while blocking the effects of more potent activators of tachycardia such as isoproterenol and CGP 12177 (see Example 2). For example, the maximal tachycardia exhibited by rat atria in the presence of Compound **2** is only about 15% of the maximal increase observed with isoproterenol (Example 2). Other beta 3 receptor agonist aryloxy propanolamines, e.g., Compounds **1** and **8**, are antagonists of tachycardia (Example 2). The structures of these aryloxy propanolamines are shown below.

Applicants have also found that the concentration ranges in which aryloxy propanolamines affect tachycardia are generally higher than the ranges in which these compounds stimulate the beta 3 receptor. For example, the $EC_{50\ Beta\ 3}$ for these beta 3 agonist aryloxy propanolamines (the concentration at which 50% of the beta 3 receptors are occupied) is generally about ten fold lower than their $EC_{50\ tachycardia}$ (the concentration which causes 50% of maximal tachycardia stimulation or inhibition), as shown in Tables 1 and 2 in Example 2. Applicants have discovered selected concentration ranges at which these aryloxypropanolamines stimulate both the beta 3 receptor and affect tachycardia. Based on these results, improved methods for treating obesity and Type II diabetes are disclosed.

As stated previously, one aspect of the present invention is an improved method for stimulating the beta 3 receptor in a subject in need of beta 3 receptor stimulation. Subjects in need of beta 3 receptor stimulation include subjects requiring treatment (therapeutic or prophylactic) for obesity or Type II diabetes. The method comprises administering to the subject

between about 1.0 to about 5.0 milligrams per kilogram of body weight per day of a compound of formula I or VIII. Preferably, between about 2.0 to about 5.0 milligrams, more preferably between about 2.0 to about 4.8 milligrams and, even more preferably, between about 3.0 to about 4.8 milligrams per kilogram of body weight per day of a compound of formulas I or VIII are administered.

The method of treating obesity or Type II diabetes disclosed herein is particularly advantageous because it can simultaneously be used to treat certain cardiac abnormalities or prevent or slow their onset. Thus, one benefit of this method is that one medication can be used to treat (therapeutically or prophylactically) patients with obesity or Type II diabetes and cardiac abnormalities characterized by abnormally rapid heart rate or irregular heart rate or the symptoms associated with such conditions.

The aryloxy propanolamines disclosed herein can modulate tachycardia in addition to agonizing the beta 3 receptor. Although Applicants do not wish to be bound by any particular mechanism, the data disclosed herein is consistent with these compounds acting at a new beta adrenergic receptor, referred to as the "beta 4 receptor", to modulate tachycardia. Specifically, these aryloxy propanolamines inhibit tachycardia to CGP 12177 in the presence of propranolol (Example 2), a beta 1 and beta 2 receptor antagonist. In addition, cardiostimulation by CGP 12177 is known to occur in both wild type and beta 3 knock-out mice, indicating that the beta 3 receptor plays little or no role in modulating tachycardia (Kaumann *et al.*, *Molecular Pharmacology* 53:670 (1998)). Based on these results, it is likely that the disclosed compounds affect tachycardia by acting at a site other than the cloned beta adrenergic receptors.

In another aspect, the methods of treatment disclosed herein can also be used to treat, prevent or slow the onset of certain cardiac abnormalities and/or to alleviate the symptoms of such cardiac abnormalities in subjects who are also in need of beta 3 receptor stimulation. Cardiac abnormalities which can be treated (prophylactically or therapeutically) by the method of the present invention are those which are characterized by, could result in and/or could cause abnormally rapid or irregular heart rate. For example, the method of the present invention can be used to slow abnormally rapid or regulate irregular heart beat. Examples of such cardiac abnormalities include arrhythmias such as atrial and ventricular tachycardia, fibrillation, flutter, and atrioventricular nodal reentry as well as cardiac dysfunctions such as angina and congestive heart failure (systolic and diastolic).

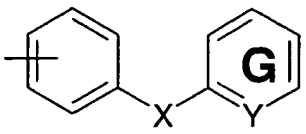
Certain compounds of the invention are particularly interesting and are preferred for the uses, methods and formulations describe herein. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

R1 is the substituted indolyl group of formula II or the substituted carbazolyl group of formula III.

R2 and R3 are both methyl.

R4 is a phenyl group substituted with one or more substituents.

R4 is a moiety of the formula VII:



VII;

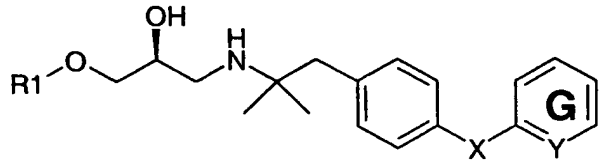
wherein:

ring **G** is unsubstituted or substituted as described above for ring **F**;

X is a covalent bond, $-CH_2-$ -O- or $-NHSO_2-$, preferably -O-; and

Y is -CH- or -N-, preferably, -N-.

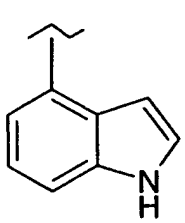
A compound of the formula VIII:

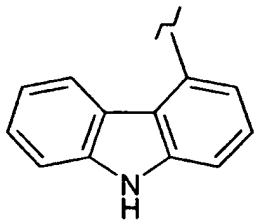


VIII;

wherein:

R1 is a moiety of the formula IX or X:





;

IX X

and X, Y and ring **G** are as defined above for the moiety of formula VII, is particularly preferred for the uses, methods and formulations described herein.

An even more preferred compound of formula VIII is one where ring **G** is substituted with -CN or $-CONH_2$. Most preferred is a compound of formula VIII wherein R1 is a moiety of formula IX and ring **G** is substituted with $-CONH_2$.

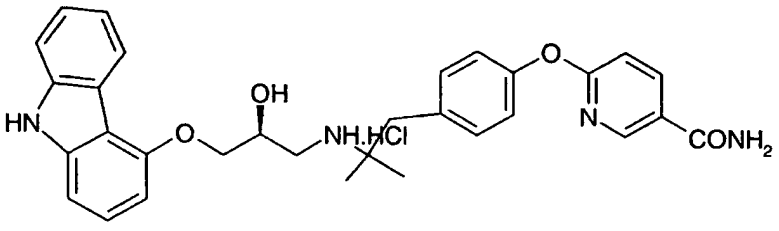
Also included for use in the present invention are physiologically acceptable salts of the compounds of formula formulas I and VIII. Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, perchloric

acid, para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

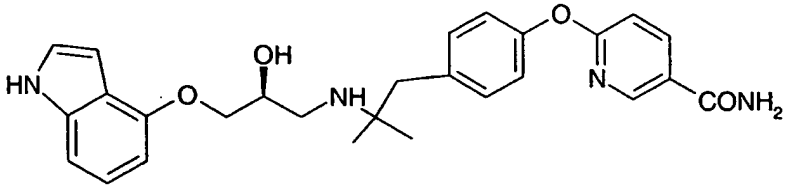
Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base or amine. Salts of acidic functional groups contain a countercation such as ammonium, sodium, potassium and the like.

The following compounds are exemplary aryloxy propanolamines which can be used in the present invention and reference numbers corresponding thereto.

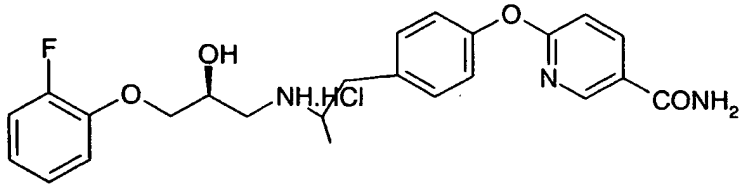
Compound 1



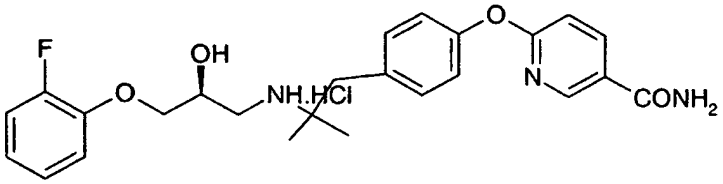
Compound **2**



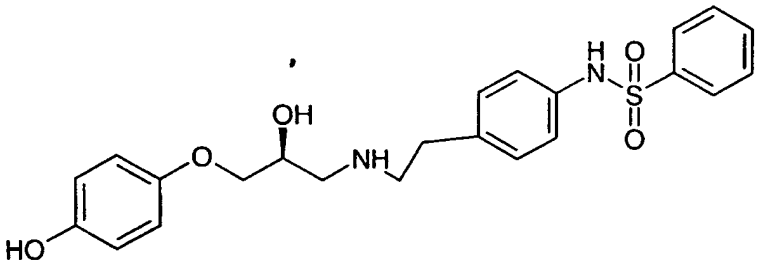
Compound **3**



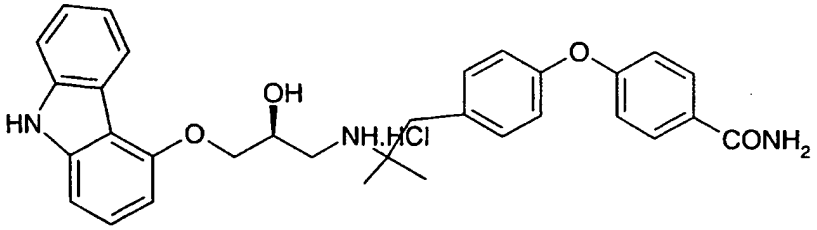
Compound **4**



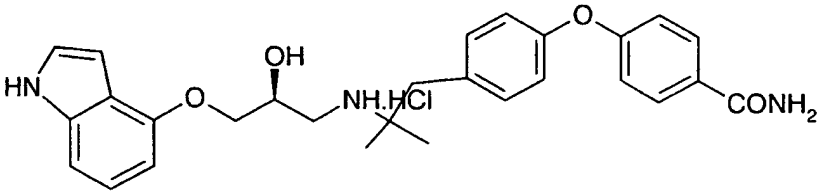
Compound **5**



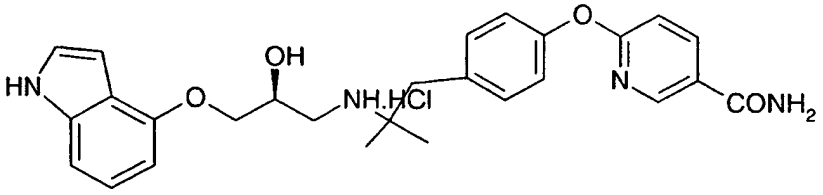
Compound **6**



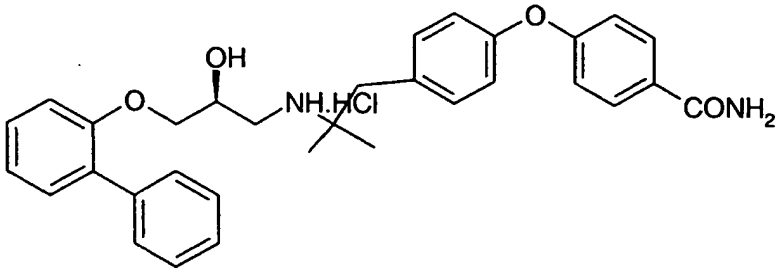
Compound **7**



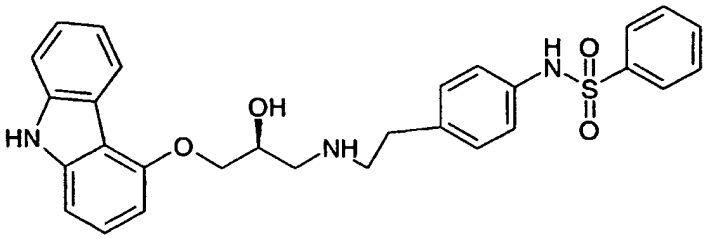
Compound **8**



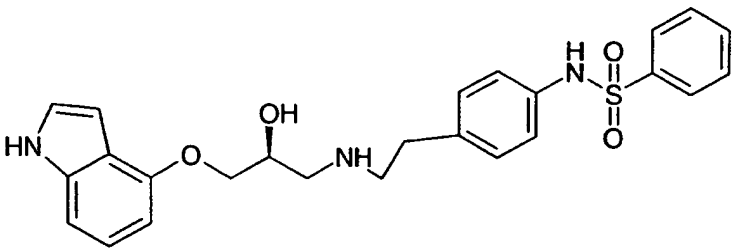
Compound **9**



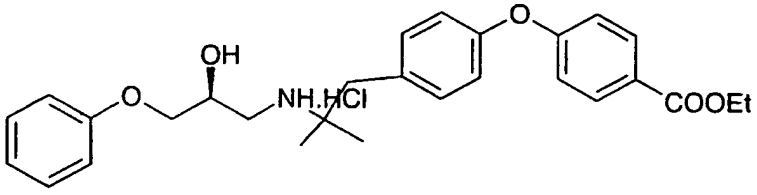
Compound **10**



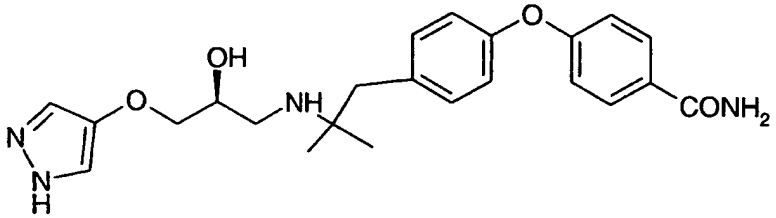
Compound **11**



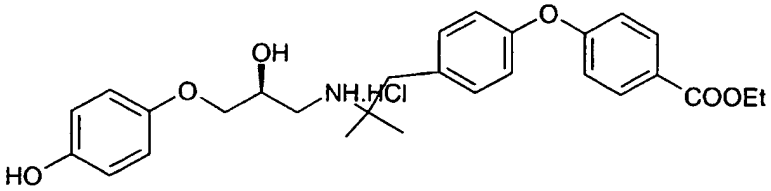
Compound **12**

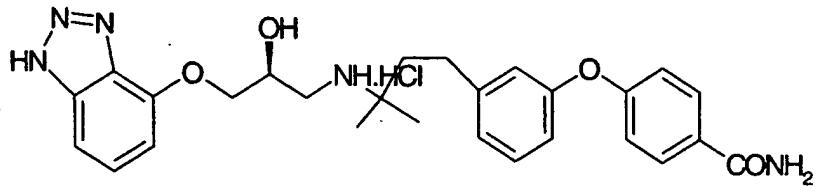


Compound **13**



Compound **14**



Compound 15 

The beta 3 agonists of the present invention can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral is a preferred mode of administration.

The beta 3 agonists can be administered to the individual in conjunction with an acceptable pharmaceutical carrier as part of a pharmaceutical composition for treatment of obesity or Type II diabetes. Formulation of a beta 3 agonist to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a

coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The beta 3 agonists of the present invention can be prepared according to procedures disclosed in WO 97/10822 to Bell *et al.*, WO 98/09625 to Crowell *et al.*, and U.S. Patent No.'s 5,808,080 and 6,046,227, the entire teachings of which are incorporated herein by reference.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - Determination of EC_{50} Values for Aryloxy Propanolamines at the Human Beta 3 Receptor

The two exon human β3 adrenergic receptor was subcloned into the BClI restriction site using a phd expression vector before transfection into the DXB-11, Chinese hamster ovary (CHO) cell line by calcium phosphate precipitation methodology. Additional details are provided in Granneman *et al.*, *Molecular Pharmacology 44:*264 (1993) and Grinnell *et al. Bio/Technology 5:*1189 (1987) the entire teachings of which are incorporated herein by reference. The stably transfected cells were grown to 95% confluency in 95% Dulbecco's modified Eagles Medium (DMEM), 5% fetal bovine serum, 0.01% proline. Media was removed and the cells were washed with phosphate buffered (pH 7.4) saline (without magnesium and calcium). Cells were then lifted using an enzyme free cell dissociation solution (Specialty Media, Lavallette, New Jersey) and pelleted by centrifugation. The cells were resuspended and added (15,000/well) to a 96-well plate. Cells were incubated at 37°C with test compounds for 20 minutes in buffer (Hank's balanced salt solution, 10 mM HEPES, 0.1% BSA, 1 mM L-ascorbic acid, 0.2% dimethyl sulfoxide, 1 mM 3-isobutyl-1-methylxanthine, pH 7.4). After

halting the incubation with quench buffer (50 mM Na Acetate, 0.25% Triton X-100, pH 5.8), the c-AMP level was quantified by scintillation proximity assay (SPA) using a modification of the commercially available c-AMP kit (Amersham, Arlington Heights, IL) with rabbit anti-cAMP antibody (ICN Biomedicals, Aurora, Ohio).

The EC_{50} was assessed as the concentration producing 50% of the maximum response to each test compound. The percent maximal response for each test compound was assessed relative to the maximal response to isoproterenol by dividing the maximal response to the test compound by the maximal response to isoproterenol x 100. The results for each compound tested are shown in Tables 1 and 2.

Example 2 - Determination of EC_{50} values and K_B Values of Aryloxy Propanolamines for Tachycardia

Male rats (approximately 300 grams) (Harlan Industries, Inc., Cumberland, Indiana, USA) were killed by cervical dislocation. Hearts were removed and the left and right atria were dissected and mounted with thread in tissue baths containing 10 mls of modified Krebs' solution. An initial optimum resting force of 1 gram was applied to the atria according to procedures described in Cohen *et al.*, *Naunyn-Schmied Arch. Pharmacol. 320*:145 (1982), the entire teachings of which are incorporated herein by reference. Tissues were allowed to equilibrate approximately 30 minutes in the presence of 3×10^{-7} M propranolol with vigorous oxygenation before exposure to drugs.

To evaluate the ability of test compounds to increase heart rate, test compounds were added cumulatively once the spontaneous atrial rate reached a steady state from the previous addition. Agonist addition was continued until no further increase in atrial rate occurred or until a concentration of 10^{-4} M was reached. The increase in beats

per minute (BPM) from baseline heart rate prior to agonist administration was measured for each concentration of agonist by means of a Beckmann Cardiotachometer or a computerized data acquisition system (BioPac Systems, Inc., Santa Barbara, CA).

The EC_{50} was assessed as the concentration producing 50% of the maximum response to each agonist. The results for each compound tested are shown in Table 1.

Table 1

	Human Beta-3		Rat Tachycardia	
Compound	%*	EC_{50} nM	E_{max}+	EC_{50} nM
1	74 ± 1	< 4	0.0	---
2	68 ± 1	7 ± 0.5	16.3	78.0
3	---	---	21.5	245.0
4	34 ± 1	18 ± 5	14.0	282.0
5	66 ± 3	8 ± 1	0.0	---
6	54 ± 3	8 ± 1	18.0	120.0
7	57 ± 3	11 ± 2	0.0	---
9	20 ± 3	20 ± 5	0.0	---
10	24 ± 3	16 ± 4	0.0	---
11	51 ± 3	47 ± 9	0.0	---
12	---	---	5.3	3100
13	70 ± 35	86 ± 8	25.0	880.0
14	78 ± 4	497 ± 126	20.6	2530
15	48 ± 3	24 ± 2	27.3	270

* Percent maximal response relative to isoproterenol (100%)

+ Maximal tachycardia in beats/minute

As can be seen from Table 1, Compounds **2-4**, **6** and **12-15** are mixed agonists/antagonists of tachycardia in rat atria, but provide less than 25% of the maximum activation caused by isoproterenol. Table 1 also shows, based on EC_{50} values, that the concentrations required to affect tachycardia are generally at least about ten fold higher than the concentrations required to stimulate the beta 3 receptor.

To evaluate the ability of test compounds to inhibit tachycardia, test compounds were evaluated by preincubation with tissue for approximately 20-30 minutes. Cumulative concentration responses to CGP 12177 were determined in the presence of test compound or vehicle. Antagonist equilibrium dissociation constants K_B were determined according to the following equation:

$$K_B = \frac{[B]}{[DR - 1]},$$

where [B] is the concentration of the test compound and dose ratio (DR) is the EC_{50} value of CGP 12177 in the presence of the test compound divided by the control EC_{50} value of CGP 12172. The K_B values are shown in Table 2 along with the human beta 3 EC_{50} values for comparison.

Table 2

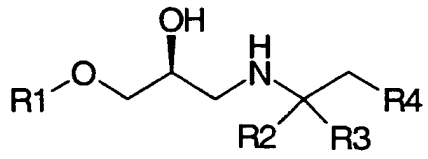
Compound	Human Beta-3 EC_{50}	Rat Tachycardia K_B
1	< 4 nM	48 nM
7	11 ± 2 nM	135 nM
8	---	35 nM
11	47 ± 9	616 nM
12	39.0 nM	1230 nM

The compounds in Table 1 having a rat tachycardia EC_{50} value of 0.0 are possible antagonists of tachycardia. Confirmed antagonists demonstrate the ability to block activation of tachycardia by agonists such as CGP 12177, as described above. Compounds **1**, **7-8** and **11-12** are confirmed antagonists of tachycardia, as shown in Table 2.

CLAIMS

What is claimed is:

1. A method for agonizing the beta 3 receptor which comprises administering to a subject in need thereof about 1.0 to about 5.0 milligrams per kilogram body weight of said subject a compound of formula I:



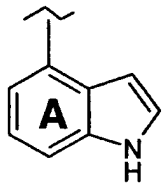
;

I;

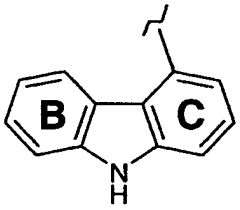
or a physiologically acceptable salt thereof,

wherein:

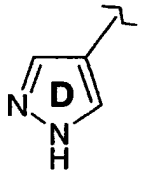
R1 is a moiety of the formula II, III, IV, V or VI:



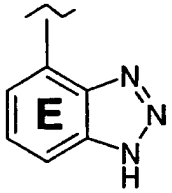
II



III



IV



V

VI

R2 and R3 are independently -H or C1-C4 alkyl;

R4 is optionally substituted phenyl provided that when R1 is a substituted moiety of formula VI, then R4 is substituted;

Ring **A** through Ring **E** are independently optionally substituted one or more times independently with a moiety selected from the group consisting of: halo, hydroxy, C1-C4

alkyl, C1-C4 haloalkyl, aryl, -CN, -COOR10, -CONHR10, -CONR10R10, -NHCOR10, -OR10, -NHR10, -SR10, $-SO_2R10$, $-SO_2NHR10$ or -SOR10;

Ring **F** is substituted with a group selected from halo, C1-C4 alkyl, hydroxyl, $-SO_2NHR5$, $-CO_2R5$, -CONHR5, $-CF_3$, $-CF_2H$, -NHCOR5 and NH(optionally substituted aryl);

R5 and R6 are independently hydrogen, C1-C4 alkyl or aryl;

R7 and R8 are independently hydrogen, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or R7 and R8 combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

R9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl or $(CH_2)_n$ optionally substituted heteroaryl;

R10 is independently hydrogen, C1-C4 alkyl or aryl; and

n is 0, 1 or 2.

2. The method of Claim 1 wherein the subject is administered about 2.0 to about 5.0 milligrams per kilogram body weight of said subject the compound.

3. The method of Claim 2 wherein the subject is being administered the compound to treat obesity or Type II diabetes.

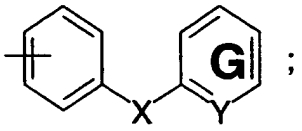
4. The method of Claim 3 wherein the subject is being administered the compound to treat a cardiac abnormality.

5. The method of Claim 3 wherein:

R2 and R3 are both methyl; and

R4 is substituted phenyl.

6. The method of Claim 5 wherein R4 is a moiety of the formula VII:



;

VII

wherein:

ring **G** is substituted or unsubstituted;

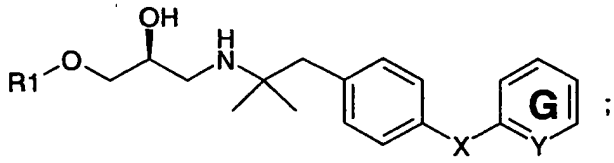
X is a covalent bond, $-CH_2-$ -O- or $-NSO_2-$; and

Y is -CH- or -N-.

7. The method of Claim 6 wherein:

R1 is a moiety of the formula II or III.

8. The method of Claim 1 wherein the administered compound is of formula VIII:



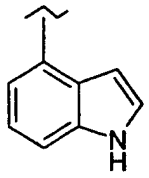
;

VIII;

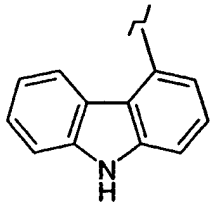
or a physiologically acceptable salt thereof,

wherein:

R1 is a moiety of the formula IX or X:



; or



;

IX IX

ring **G** is substituted or unsubstituted;

X is a covalent bond, $-CH_2-$ -O- or $-NSO_2-$; and

Y is -CH- or -N-.

9. The method of Claim 8 wherein the subject is administered about 2.0 to about 5.0 milligrams per kilogram body weight of said subject the compound.

10. The method of Claim 9 wherein the subject is being administered the compound to treat obesity or Type II diabetes.

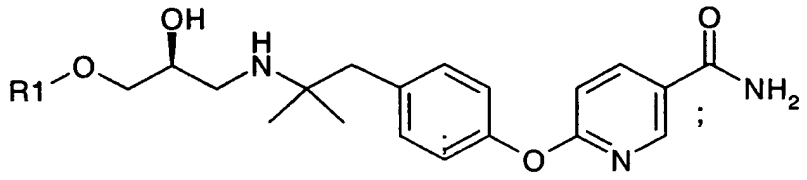
11. The method of Claim 10 wherein the subject is being administered the compound to a cardiac abnormality.

12. The method of Claim 10 wherein -X- is -O- and ring **G** is substituted with $-CONH_2$ or -CN.

13. The method of Claim 12 wherein R1 is a moiety of formula IX, ring G is substituted with -CONH2, and Y is -N-.

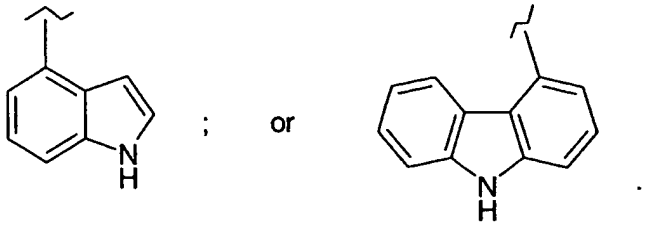
14. A method for treating obesity or Type II diabetes which comprises administering to a subject in need thereof about 1.0 to about 5.0 milligrams per kilogram body weight of said subject a compound of formula I, as defined in Claim 1, or a physiologically acceptable salt thereof.

15. The method of Claim 14 wherein the compound administered is of the formula:



;

or a physiologically acceptable salt thereof, wherein R1 is a moiety of the formula IX or X:



IX ; or X.

16. The method of Claim 15 wherein the subject is administered between about 2.0 milligrams per kilogram body weight to about 5.0 milligrams per kilogram body weight of the compound.

17. The method of Claim 16 wherein the subject is being administered the compound to treat a cardiac abnormality.

18. The method of Claim 15 wherein R1 is a moiety of the formula IX.

19. A use of a compound of formula I, as defined in Claim 1, or a physiologically acceptable salt thereof, in the preparation of a medicament adapted for agonizing the beta 3 receptor or for treating obesity or Type II diabetes characterized in that the medicament is such as to provide from about 1.0 milligrams per kilogram body weight to about 5.0 milligrams per kilogram body weight to a subject.

20. A pharmaceutical composition containing a compound of formula I, as defined in Claim 1, or a physiological salt thereof, adapted for administration of about 1.0 milligrams per kilogram body weight to about 5.0 milligrams per kilogram body weight in order to stimulate the beta 3 receptor or to treat obesity or Type II diabetes.